REMARKS

Claims 36-78, 88-122, 128-145, and 147-161 are pending in the application. Claims 70-78, 88, 96-107, 115-118, 139-145, 147, 151-155, are withdrawn from examination as directed to a non-elected invention. Claims 68, 69, 88, 90-92, 108-114, 119, 137, 138, 147, 149, 156-159, and 161 are withdrawn from examination as directed to a non-elected species. Claims 63-67, 89, 93-95, 120-122, 128-136, 148, 150, and 160 are under examination on the merits to the extent that they read on the elected species, designated as recombinant RSV with a SH gene or genome segment deletion. By this submission, claim 120 has been amended for clarity in accordance with the Office's suggestions. This amendment is fully supported by the disclosure and no new matter has been added to the application.

Information Disclosure Statement

The Office has acknowledged receipt of the Information Disclosure Statements filed on July 7, 2000 (Paper No. 7) and December 8, 2000 (Paper NO. 11). Applicants further note that the Office has not yet considered the references from Paper No. 7 due to present unavailability of the parent file in the PTO. Applicants respectfully request that the references from Paper No. 7 be considered in the next Action without prejudice to Applicants ability to respond to any new rejections raised based on these references.

Double Patenting

Claims 131 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 23, 24, and 62 of copending Application No. 09/291,894. The Office contends that, although the conflicting claims are not identical, they are not patentably distinct from each other because the conflicting claims are drawn to recombinant RSV comprising RSV with sequences of different subgroups (A and B) and an SH gene deletion.

Applicants note that this is a provisional obviousness-type double patenting rejection, and respectfully defer their response to the merits of the rejection until the allegedly conflicting claim(s) in one of the subject cases is/are allowed.

Claim Objections

Claim 120 is objected to under 37 CFR 1.75(c), as allegedly being of improper dependent form for failing to further limit the subject matter of a previous claim. In accordance with the Office's suggestions, Applicants have amended the subject claim for clarity to place the claim in proper dependent form. In particular, amended claim 120 is now drawn to the RSV of claim 63, "which is a complete virus". As is clearly denoted in the specification and original claims, the "respiratory syncytial virus" of claim 63 is directed to an isolated infectious viral particle which comprises, at a minimum, the N, P, L and polymerase elongation factor proteins. As such, this basic virus particle is viable and infectious without the inclusion of non-essential components of a "complete" RSV. In contrast, as is also disclosed in the specification, it is within the scope of the invention to provide recombinant RSV that comprise essentially complete viruses, i.e., with all essential viral components and further including non-essential components as found in a complete, e.g., wild-type, RSV. Clearly representative of these teachings, the specification teaches that a number of non-essential genes, for example the SH, NS1 and NS2 genes, "can be ablated or otherwise modified to yield desired effects on virulence, pathogenesis, immunogenicity and other phenotypic characters. For example, ablation by deletion of a non-essential gene such as SH results in enhanced viral growth in culture." (see, e.g., page 38, lines 13-19).

In view of the foregoing remarks, the objection to claim 120 is believed to be obviated.

Patentability Under 35 U.S.C. § 112, First Paragraph

Claims 128-131 stand rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. The Office Action sets forth a number of general caveats that are asserted to render the invention impracticable without "undue experimentation." In particular, the Office contends that "[t]he art teaches that RSV vaccines comprising live attenuated virus often do not confer protection against subsequent RSV infection due to factors such as maternally acquired serum antibodies, incomplete immunity, and the

existence of multiple antigenically diverse strains. (citing Murphy et al., Virus Res. 32:13-36, 1994, especially pages 14-15 and page 22, last partial paragraph, through page 26, first paragraph). In addition, the Office states that:

> The disclosure teaches how to make recombinant RSV having a deletion of the SH gene (see Example XIII beginning at page 161) and how to elicit an immunogenic response in BBB/c mice by administration of the mutant RSV. However, the disclosure does not teach that the immunogenic response is protective in humans against subsequent RSV infection in the presence of passively acquired maternal antibodies or that it is protective against multiple strains of human RSV.

Finally, the Office asserts that "[b]ecause the claims are drawn to vaccine compositions for protection against RSV in humans and because the art teaches that attenuated RSV vaccines are not protective against all subsequent RSV infections, it would require undue experimentation by one of skill in the art to be able to practice the claimed invention."

Applicants respectfully traverse the foregoing grounds of rejection and submit that the teachings of the specification fully enable the artisan to practice the invention in a manner that is "reasonably commensurate" with the scope of the claims presented for review.

As an initial point in rebuttal to the Office's evidence and reasoning directed to the issues of enablement, Applicants respectfully submit that the appropriate standard for efficacy of a human vaccine does not require prevention of all subsequent infections by all possible variants of a pathogen in all human populations. On the contrary, the enablement requirement of 35 U.S.C. § 112 only requires that there be a "reasonable correlation" between the disclosure and the scope of protection sought in the claims, having due regard for the nature of the invention and the state of the art. (See, e.g., In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991); Ex parte Jackson, 217 USPQ 804, 807 (Bd.Pat.App.Int. 1982); In re Fisher, 166 USPQ 18, 24 (CCPA 1970); MPEP § 706.03(n)). The proposed requirement for an optimal, comprehensively effective vaccine is also contrary to the central policy of U.S. patent law--to promote the useful arts. This policy is particularly permissive in the context of biomedical inventions such as human

vaccines. As emphasized by the Board in Ex parte Aggarwal, 23 USPQ2d 1334 (Bd. Pat. Appl. Inter. 1992):

> Case law subsequent to Brenner is receptive to early filing of applications in the biomedical field . . .. (citing Brenner v. Manson, 383 U.S. 519 (1966)).

In the present field of invention, the artisan will not expect that useful vaccines are to be 100% effective in a single dose for all populations covering all potential variants of a targeted pathogen. On the contrary, the various obstacles to this goal proposed by the Office are anticipated, and accepted as "reasonable" and "ordinary" hurdles to the clinical refinement of all vaccine formulations and protocols. These refinement efforts do not rise to the level of "undue experimentation", particularly when the goal of the artisan is to implement a pioneering vaccine as provided by Applicants to ameliorate such a significant threat to human health as RSV.

Merely because the Office can point to certain obstacles that might render an embodiment of the claimed vaccine viruses inoperable in some instances--to comprehensively prevent all variants and manifestations of RSV--such obstacles do not support a finding of "undue experimentation." The Office rests its conclusion on certain passages of the Murphy et al. reference that discuss the complications of maternally acquired antibodies, incomplete immunity, and multiple, antigenically diverse RSV strains. A more in-depth analysis of this reference undermines the Office's conclusion of undue experimentation. In particular, the Murphy et al. reference addresses each of the obstacles advanced by the Office and provides solutions that parallel the teachings and guidance provided in Applicants' disclosure. Thus, Murphy et al. teaches at page 22, last paragraph, to page 23, as follows:

> First, live RSV vaccines would be anticipated to stimulate an immune response that resembles the response to wild-type virus infection, including the induction of serum and mucosal antibodies that are able to protect both the upper and lower respiratory tract, as well as the stimulation of a balanced immune response. Second, infection and immunization in the presence of maternal antibodies is possible, since wild-type RSV can infect and replicate efficiently in infants possessing substantial titers of residual maternally-acquired serum antibodies. Third, immunization of RSV-seronegative infants with live

> attenuated RSV vaccines was not associated with disease potentiation during subsequent natural RSV infection in the vacinees.
>
> How will a live attenuated vaccine induce resistance when wild-type infection itself, in some instances, fails to prevent serious illness during a second infection, especially considering that the immunity induced by live attenuated virus infection is likely to be weaker than that induced by wild-type virus infection? There are two answers to this important question. First, because a single dose of a live virus vaccine will not be sufficient to achieve a high level of immunity, the vaccine will need to be given several times during the first few months of life. Data in the literature suggest two infections with wild-type virus are needed to ensure a durable serum and local antibodyu response, and this is a partial explanation for the greatly decreased incidence of severe RSV desease during a third or subsequent RSV infection. . . . The optimal schedule will have to be determined by experimentation, but it might require two immunizations within the first two months of life. Fortunately, the immunization procedure will be trivial, involving the application of nose drops containing live vaccine virus. Second, since two antigenically distinct subgroups of RSV exist, the live RSV vaccine will likely be a bivalent vaccine. Reinfection with disease reflects not only waning immunity to the first RSV infection, but also antigenic diversity when the second infection virus is of the heterologous RSV subtype. Thus, multiple administrations of a bivalent RSV subgroup A and B vaccine during the first several years of life will be needed to induce a sustained level of serum and mucosal antibodies that will protect against severe RSV bronchiolitis and pneumonia in infancy and early childhood. (citations omitted, underscores added).

In summary, Murphy et al. do not forecast that development of a live-attenuated RSV vaccine would be attended by "undue experimentation." On the contrary, the solutions offered by Murphy et al. fall directly in line with Applicants' teachings and are squarely within the grasp of the skilled immunologist to implement. For example, the presence of maternal antibodies will be addressed by booster immunization in refractory patient populations. This course of clinical refinement is clearly disclosed in Applicants' specification. In addition, the specification provides extensive, detailed guidance on how to achieve a fine-tuned balance between attenuation

and immunogenicity for the claimed vaccine candidates, and how this balance will be manipulated and validated for different patient populations.

With respect to the existence of multiple, antigenically diverse RSV strains, this variation by no means represents an "undue" challenge in the highly skilled disciplines of virology and vaccine development. On the contrary, the Murphy et al. reference closely accords with Applicant's teachings on this subject, which guide the artisan toward a multivalent vaccine strategy that combines both RSV A and RSV B specific components within a single vaccine formulation or coordinate administration protocol.

The burden is on the Office to establish a *prima facie* case of nonenablement against Applicants' vaccine-related claims, and this burden is substantial. It is not sufficient to cite a handful of obstacles that might preclude a comprehensively effective, or optimal vaccine within the scope of the claims presented for review. Rather, the Office must demonstrate that Applicants' disclosure, complemented by available knowledge and skill in the art, is facially inadequate to enable the artisan to practice the invention in a manner "reasonably commensurate with the scope of the claims" without "undue experimentation."

As emphasized by the Federal Circuit's predecessor court in In re Marzocchi et al. (169 USPQ 367 CCPA 1971), all patent disclosures are entitled to a presumption that they satisfy the enablement requirement. This presumption is only overcome by scientific evidence that is "inconsistent with" the disclosure's teachings. . As further explained in the PTO's Enablement Guidelines, (see, e.g. Example 5E: "Peptides for Treating Obesity"):

> The Office must accept as being true the statements supporting enablement unless there is an objective reason, usually supported with documentary evidence, to question them.

Enablement is also not defeated by a requirement for experimentation to practice an invention in the manner claimed. In fact, "a considerable amount of experimentation is permissible," so long as the experimentation is not "undue." Ex parte Jackson, 217 USPQ 804, 807 (Bd. Pat. App. Int. 1982). The determination of what

constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. This test is not merely quantitative and a considerable amount of experimentation is permissible, provided that the specification offers a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. (id., citations omitted). As explained in the case of In re Michalek, 34 CCPA 1124 (1947):

> Skilled workers would as a matter of course, in our opinion, if they do not immediately obtain desired results, make certain experiments and adaptations . . ..

Likewise, in the case of In re Angstadt and Griffin, 190 USPQ 214, 219 (CCPA 1976), the court emphasized that:

> In this art the performance of trial runs using different catalysts is "reasonable," even if the end result is uncertain, and we see no reason on this record why appellants should not be able to claim as their invention the broad range of processes which they have discovered. (emphasis supplied).

With respect to the issue of animal model data, the Office acknowledges that the disclosure provides recombinant RSVs that exhibit desired phenotypic activities of attenuation and immunogenicity sufficient to elicit an immunogenic response in murine subjects. Nonetheless, the Office asserts that the disclosure "does not teach that the immunogenic response is protective in humans against subsequent RSV infection in the presence of passively acquired maternal antibodies or that it is protective against multiple strains of human RSV." Issues raised by this statement have largely been addressed in the preceding paragraphs. The additional question with regard to the predictive value of animal model data is therefore the sole remaining enablement issue that calls for resolution.

To clarify this issue, Applicants note again that the burden to establish nonenablement of the subject claims is on the Office. In this regard, the Office's Enablement Guidelines state, at section III(A)(2), that:

> Since the initial burden is on the examiner to give reasons for the lack of enablement, when possible to supported (sic) by evidence, the examiner must also give reasons for a

> conclusion of lack of correlation for an in vitro or in vivo animal model example. A rigorous or an invariable exact correlation is not required. (citing Cross v. Lisuka, 224 USPQ 739, 747 (Fed. Cir. 1985), emphasis added).

It is clear from this authority that Applicants' murine model data need not be precisely reflective of the activity of a recombinant RSV vaccine candidate in humans in order to fulfill the enablement requirement. On the contrary, the PTO's Enablement Guidelines (see, e.g., Example 5E: "Peptides for Treating Obesity," at page 46) further specify that data from animal testing merely must be "reasonably correlative to treatment in other mammals . . . based on the state of the art."

To further clarify this issue, Applicants respectfully direct the Office's attention to the holding in Ex parte Aggarwal, 23 USPQ2d 1334 (Bd. Pat. Appl. Inter. 1992) where the Board noted:

> Case law subsequent to Brenner is receptive to early filing of applications in the biomedical field so long as the patent applicant, when properly challenged by the examiner, can provide evidence showing substantial activity in screening tests customarily used and accepted as predictive of human activity . . .. All that is required is that there be a "reasonable correlation" between the animal model results and projected activity in humans. (referencing Brenner v. Manson, 383 U.S. 519 (1966), emphasis added).

Applying this authority to the present facts, Applicants have disclosed the use and results of customary assays employing *in vitro* and murine model subjects to demonstrate key phenotypic characteristics of the recombinant RSV vaccine candidates of the invention. These characteristics, namely viability, attenuation, and immunogenicity, each are accepted in the art as correlating reasonably with the corresponding activity of RSV vaccine candidates in humans.

A brief review of the published literature clearly validates the use of murine models to predict general activities of RSV vaccine candidates in humans. RSV model data conventionally follows a progression of in vitro assays, followed by rodent model studies, followed by non-human primate trials, and human clinical trials. Reflective of this widely accepted course of validation, Kim et al. (Pediatrics 52:56/72-62/78, 1973, copy to be provided under separate cover) report that a temperature sensitive

(*ts*) RSV mutant was selected for human studies based on *in vitro* and subsequent rodent trials, leading to the human testing. In particular, the reference states that:

> This strain, designated as RS-A2, ts-1, was chosen on the basis of its behavior *in vitro* in tissue culture and in vivo in the hamster host and in human volunteers. This mutant did not produce plaques, i.e., did not initiate foci of infection, at or above 37C in cell culture, unlike wild type virus which produced plaques without restriction at 39C. In the hamster, infection with the mutant was limited to the cooler upper respiratory tract (32C to 34C) and virus was not found in the lungs where the temperature was 37C. . . . The mutant infected adult volunteers when administered into the nasopharynx without producing disease and induced resistance to subsequent challenge with virulent wild type virus. (page 56/72-57/73)

From this report, it is clear that *in vitro* and rodent subjects are art-accepted models for general prediction of RSV characteristics in humans, and that data from these models are "reasonably correlative" with activity (e.g., attenuation and immunogenicity) in humans.

A subsequent report by Murphy et al., (Virus Res. 32:13-36, 1994, copy to be provided under separate cover), details a similar course of validation testing for RSV vaccine candidates (including the biologically derived cpts-530, and cpts-248 strains bearing attenuating point mutations that were identified and incorporated by Applicants into recombinant RSV vaccine candidates)

> Nine mutants of *cp*-RSV, which had acquired either the ts or small plaque (*sp*) phenotype, were generated by chemical mutagenesis with 5-fluoracil. The two ts mutants with the lowest in vitro shut-off temperature, namely the *cpts*-248 (38°C) and *cpts*-530 (39°C) mutants, were the most restricted of the nine *cp*-RSV mutant progeny in replication in Balb/c mice. In seronegative chimpanzees, the *cpts*-248 mutant replicated 4-fold less efficiently in the nasopharynx and cause significantly less rhinorrea than its *cp*-RSV parent. The *cpts*-248 mutant virus, like its sp-RSV parent, was 1000-fold restricted in replication in the trachea compared to wild-type RSV. . . . The *cpts*-248 mutant was immunogenic and induces a high level of resistance in chimpanzees to subsequent challenge with wild-type RSV. The *cpts*-248 mutant therefore exhibits a set of properties that make it a promising vaccine candidate. (page 25, first

full paragraph)

In a related report from the same lab, Crowe et al. (Vaccine 13:847-855, 1995, copy to be provided under separate cover) present additional studies tracking characteristics of viability, attenuation, and immunogenicity between *in vitro* subjects, BALB/c mice, seronegative chimpanzees, and chimpanzees infused with RSV antibodies prior to immunization. The data from these trials are clearly presented as reasonably correlative between the different model subjects for the subject activities.

The art clearly accepts chimpanzees as closely faithful model subjects to humans with respect to their permissiveness and responses to RSV infections, and this has not been challenged by the Office. The further validation of the tractability between murine, through chimpanzee, to human subjects is nonetheless well documented in the literature. For example, the foregoing validation trials have been carried forward in a related report by Wright et al. (J. Infect. Dis. 182:1331-1342, 2000) detailing clinical trials for a multiply-attenuated RSV vaccine candidate, related to cpts-248, designated cpts-248/404 (also bearing attenuating point mutations that were identified and incorporated into recombinant RSV vaccine candidates by Applicants). In this report:

> A live-attenuated, intranasal respiratory syncytial virus (RSV) candidate vaccine, cpts-248/404 was tested in phase 1 trials in 114 children, including 37 1-2-month-old infants—a target age for RSV vaccines. The cpts-248/404 vaccine was infectious at 10^4 and 10^5 plaque-forming units in RSV-naïve children and was broadly immunogenic in children 6 months old. . . . [t]here was restricted virus shedding on challenge with a second vaccine dose and preliminary evidence for protection from symptomatic disease on natural reexposure. (Abstract).

With respect to SH gene deletion mutants of RSV, the foregoing evidence relating to *ts* attenuated RSV also validates the use of animal models for the instantly claimed RSV vaccine candidates. Applicants' *in vitro* and murine data for their SH deletion recombinant viruses are therefore respectively submitted to be reasonably correlated with the projected activity of the viruses in non-human primate and human subjects. It is the Office's burden to provide direct evidence contrary to this assertion in order to sustain the instant enablement rejection. In this regard, Applicants respectfully

direct the Office's attention to a more recent publication from the inventor's lab (Whitehead et al., J. Virol. 73:3438-3442, 1999, copy to be provided under separate cover) that describes further phenotypic validation of SH deletion (and NS2 deletion, with and without attenuating point mutations represented in *cpts*-248/404) RSV vaccine candidates. In particular, this report details the extension of Applicants' murine studies to chimpanzee subjects and demonstrates that:

> Recombinant virus rA2ΔNS2 replicated to moderate levels in the upper respiratory tract, was highly attenuated in the lower respiratory tract, and induced significant resistance to challenge with wild-type RSV. The replication of rA2ΔSH was only moderately reduced in the lower, but not the upper, respiratory tract. However, chimpanzees infected with either virus developed significantly less rhinorrea than those infected with wild-type RSV. These findings demonstrate that a recombinant RSV mutant lacking either the NS2 or SH gene is attenuated and indicate that these deletions may be useful as attenuating mutations in a new, live recombinant RSV vaccine candidates for both pediatric and elderly populations. The SH mutation was incorporated into a recombinant form of the spts-248/404 vaccine candidate, was evaluated for safety in seronegative chimpanzees, and can now be evaluated as a vaccine for humans. (Abstract, underscores added).

The foregoing reports clearly evince that murine model studies are widely accepted in the art as reasonably predictive of RSV activity in non-human primate and human subjects. In this regard, the precise level of viability, attenuation and/or immunogenicity is not at issue. On the contrary, the artisan is mindful of consistent, predictable differences between each accepted animal model subject, and between these models and human subjects. Thus, mice and other rodent model subjects are known to be considerably less permissive for RSV infection than, for example, chimpanzees and humans. This knowledge complements the artisan's ability to extrapolate findings between different subject populations. Thus, while Applicant's animal model data may not be "conclusive" of specific vaccine efficacy for all populations of humans and covering all RSV subtypes and strains, they are clearly "reasonably correlative to treatment in other mammals . . . based on the state of the art." (PTO Enablement Guidelines, supra).

In summary, Applicants submit that the level of skill in the present arts of molecular immunology and vaccine development is high. The skilled artisan is equipped with extensive tools and training with which to implement and adapt Applicants' teachings to produce and select operable vaccine candidates that are fully commensurate with the scope of the claims presented. This guidance provided by Applicants' disclosure contemplates all necessary steps to refine RSV SH deletion mutant vaccine candidates for use in single or multiple patient populations, including seronegative and seropositive infants, and against single or multiple RSV subgroups, without undue experimentation. For these reasons, withdrawal of the rejection of claims 128-131 under 35 U.S.C. § 112, first paragraph, is earnestly solicited.

Patentability Under 35 U.S.C. § 112, Second Paragraph

Claim 121 is rejected under 35 U.S.C. 112, second paragraph, for allegedly being indefinite. Specifically, the Office notes that claim 121 is drawn to a subviral particle, while claim 63 from which claim 121 depends recites a virus. The Office asserts that the term "virus" denotes "a complete virion", and that it is therefore unclear how a complete virion or virus can also be a subviral particle. Applicants respectfully traverse.

As noted above in regard to the objection to claim 120, Applicants have amended claim 120 herein for clarity to specify that the subject, dependent species within the scope of claim 63 "is a complete virus". The specification and original claims teach and recite an isolated infectious viral particle which comprises, at a minimum, the N, P, L and polymerase elongation factor proteins. Consistent with this terminology, the invention encompasses both complete viral particles and "subviral" particles, which will be understood to include viable, infectious recombinant RSV engineered to lack one or more non-essential components of a "complete" RSV. As also noted above, the specification adds clarity to these terms by specifically disclosing recombinant viruses engineered to lack one or more genes or genome segments, exemplified by gene deletion or expression mutations in SH, NS1 and NS2. In particular relation to the presently elected invention, the disclosure teaches that the incomplete, "SH minus virus grows well in tissue culture and exhibits site-specific attenuation in the upper respiratory tract." (page 174, lines 28-30).

Considering the foregoing evidence and remarks, Applicants respectfully submit that the subject matter of claim 121 is conveyed with sufficient clarity, and therefore request that the rejection of claim 121 under 35 U.S.C. 112, second paragraph, be withdrawn.

Patentability Under 35 U.S.C. § 103

Claims 63-67, 89, 93-95, 120, 121, 128, 131-136, and 150 are rejected under 35 U.S.C. § 103 as allegedly obvious over Collins et al. (Proc. Natl. Acad. Sci. USA, 92:11563-11567, Dec. 1995).

The Office characterizes the present invention as providing a recombinant

respiratory syncytial virus (RSV) comprising a major nucleocapsid (N) protein, a nucleocapsid phosphoprotein (P), a large polymerase (L) protein, and an RNA polymerase elongation factor. The recombinant genome or antigenome comprises a partial or complete (SH) gene deletion, which is optionally further modified by one or more attenuating mutations adopted from one or more biologically derived mutant RSV strains, and alternatively stabilized by multiple nucleotide changes in the codon specifying the mutation. The invention is further characterized to embrace immunogenic compositions comprising these recombinant RSVs for eliciting an immune response against both RSV subgroups, A and B, and isolated polynucleotides comprising the modified recombinant RSV genome or antigenome.

The Office cites Collins for allegedly teaching infectious recombinant RSV comprising a major nucleocapsid (N) protein, a nucleocapsid phosphoprotein (P), a large polymerase (L) protein, and an RNA polymerase elongation factor, "wherein defined changes can be introduced for development of live attenuated vaccine strains" (citing the abstract). The Office further contends that:

> Collins suggests that deletion or modification of specific genes, such as the SH gene, may result in attenuated RSV strains with enhanced immunogenicity and a higher level of protection against RSV infection than wild-type virus.

In addition, the Office cites Collins for ancillary teachings relating to a proposed combination of RSV subgroup B genes with a RSV A genome to broaden the immune response to cover multiple RSV strains in a population, and relating to stabilization of mutant RSV strains by incorporation of two or more nucleotide and amino acid substitutions (see page 11566, column 2, first full paragraph).

Based on the foregoing interpretation of Collins et al., the Office concludes that the invention as characterized above would have been *prima facie* obvious over the reference.

Applicants respectfully traverse the foregoing grounds for rejection and submit that the subject matter of claims 63-67, 89, 93-95, 120, 121, 128, 131-136, and 150 is not rendered obvious by the Collins et al. reference.

Applicants respectfully submit that the Office's construction of the Collins et al. reference is inconsistent with the actual teachings of the reference, as they would be

read by the artisan of ordinary skill and in view of applicable legal precedent governing the relevant standard of review. In particular, the Office construes Collins et al. as directly teaching that "defined changes can be introduced for development of live attenuated vaccine strains." This interpretation presupposes that Collins et al. actually forecast a reasonable expectation of success for introducing significant genetic changes (e.g., attenuating point mutations and/or deletion of selected RSV genes), to yield live-attenuated vaccine candidates. This supposition is directly contravened by the full teachings of the cited reference.

In particular, Collins et al. teach that defined mutations may be introduced into a recombinant RSV. However, the reference prophesies a myriad of possible permutations in recombinant RSV, and does not forecast with any specificity or actual working examples what changes will be effective, and the actual result of such changes would be. Thus, the statements in the reference that are relied upon by the Office, at best, suggest that it may be "obvious to try" a broad laundry list of potential mutations in recombinant RSV with the hope of determining a fruitful path for further investigation.

As such, the reference fails to provide the requisite "practical motivation" and specific guidance to raise the disclosure beyond what the courts have characterized as "an invitation to experiment." This interpretation is validated by more detailed teachings within the Collins et al. reference, as set forth in the Discussion section. In particular, the reference states at page 1156 (left column last paragraph, bridging to right column) that:

> The ability to introduce defined mutations into infectious RSV should have many applications in extending analyses of RSV molecular biology and pathogenesis. For example, the functions of the RSV proteins, especially the NS1, NS2, SH, M2(ORF1), and M2(ORF2) proteins, could be investigated by introducing mutations that ablate or reduce their level of expression or that yield mutant protein. (emphasis supplied).

Additional teachings of Collins et al. further clarify that this report was intended, and understood in the art, to provide only an invitation to experiment--leaving it to future investigations to provide specific, practical directions and guidance to arrive at actual working embodiments. Exemplifying this message, the authors conclude their Discussion with the following statements: "An exciting possibility is that RSV might be engineered in ways that enhance its immunogenicity and induce a level of protection

greater than that provided by natural infection." (page 1167, last paragraph) "Also, it should be possible to explore other methods of attenuation." (page 1165, right column, last partial paragraph). (underscore added).

These teachings clearly reflect an "obvious to try" form of disclosure. As articulated by the District Court in Merck and Co. Inc. v. Danbury Pharacal, Inc., 8 USPQ2d 1793, 1816 (D. Del. 1988) (quoting and citing, respectively, In re Fine, 5 USPQ2d 1596, 1599, (Fed. Cir. 1988), and In re Merck, 231 USPQ 375, 379-80 (Fed. Cir. 1986)):

> [T]he governing standard is emphatically not whether a particular methods or process leading to an invention would be "obvious to try", but whether such an experiment would have been expected to succeed.

To determine what constitutes a "reasonable expectation of success" in this context, the Federal Circuit's predecessor court stated in In re Gyurik, 201 USPQ 552, 557 (CCPA 1979) that:

> An element in determining obviousness of a new chemical compound is the motivation of one having ordinary skill in the art to make it. That motivation is not abstract, but practical, and is always related to the properties or uses one skilled in the art would expect the compound to have, if made.

In the instant case, the Office relies upon Collins et al. for allegedly teaching that "defined changes can be introduced for development of live attenuated vaccine strains." This construction infers a definite disclosure of particular modifications that should be made in a recombinant RSV, and further supposes that there is a scientifically reasonable forecast that these specific changes will yield "live attenuated vaccine strains".

What in fact the present record shows, is that Collins et al. provide a tentative laundry list of "possible" mutations that "could be investigated" or "should be possible to explore". By these statements, the reference facially precludes a determination of any specific guidance and practical motivation to make the selected changes specified in Applicants claims. Nor does the reference provide positive evidence or specific guidance to convince the artisan to undertake the manipulations provided as working examples in Applicants' disclosure (e.g., identifying and then introducing

multiple attenuating point mutations, selecting and constructing deletions of genes having entirely unknown functions)—with the necessary "reasonable expectation" that such significant changes would lead to successful recovery of viable, attenuated, immunogenic vaccine candidates as taught by Applicants.

Applying controlling legal authority to the foregoing facts, it is clear that the Office's alleged case of *prima facie* obviousness fails. The Collins et al. reference does not teach with practical and specific motivation the particular mutations and combinations of mutations covered by Applicants' claims. Similarly, the reference fails to provide a reasonable expectation of success that such changes will yield the results disclosed in Applicants specification. This fact scenario squarely fits the analysis provided by the Federal Circuit in In re O'Farrell,

> [i]n some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication or which parameters were critical or no direction as to which of many possible choices is likely to be successful." 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

In view of the foregoing evidence and legal authority, Applicants respectfully request that the rejection of claims 63-67, 89, 93-95, 120, 121, 128, 131-136, and 150 under 35 U.S.C. § 103 over Collins et al. be withdrawn.

Claims 122, 129, and 130 are rejected under 35 U.S.C. 103(a) as being unpatentable over Collins et al. in view of Randolph et al. (EPA 0 567 100). Collins et al. is relied upon by the Office as set forth above. Randolph et al. is secondarily cited for teaching intranasal administration of an aerosol containing 10^6 PFU of attenuated infectious RSV for eliciting systemic immunity. Combining these alleged teachings, the Office contends that it would have been prima facie obvious to administer the recombinant RSV taught by Collins et al. via the dosage and route taught by Randolph et al.

Applicants respectfully traverse this rejection on the basis that Collins et al. is a defective primary reference and does not disclose the recombinant RSV as alleged by the Office. The reasons in support of this position are set forth in detail above. For these reasons, the proposed combination of the RSV vaccine as allegedly taught by

Collins et al. with a delivery mode as allegedly taught by Randolph et al. is obviated as a basis for rejecting the subject claims. Withdrawal of the rejection of claims 122, 129, and 130 under 35 U.S.C. 103(a) is therefore earnestly solicited.

Claim 160 is rejected under 35 U.S.C. 103(a) as being unpatentable over Collins et al. in view of Klein et al. (WO 93/14207). Collins et al. is relied upon by the Office as set forth above. Klein et al. is secondarily cited for teaching "multimeric hybrid genes" comprising gene sequences from RSV and PIV, and that recombinant antigens encoded by such hybrid genes are capable of protecting infants and other susceptible individuals against both RSV and PIV. On this basis, the Office contends that it would have been obvious to incorporate a PIV gene or gene segment into an infectious recombinant RSV as allegedly taught by Collins et al. to elicit an immunogenic response against both pathogens by administration of a single virus.

Applicants respectfully traverse this rejection on the basis that Collins et al. is a defective primary reference and does not disclose the recombinant RSV as alleged by the Office. The reasons in support of this position are set forth in detail above. For these reasons, the proposed combination of the RSV vaccine as allegedly taught by Collins et al. with a multivalent vaccine construction as allegedly taught by Klein et al. is obviated as a basis for rejecting the subject claim. Withdrawal of the rejection of claim 160 under 35 U.S.C. 103(a) is therefore respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe that all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-332-1380.

Respectfully submitted,

Date: November 9, 2001

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

120. (Amended) The recombinant RSV of claim 63 which is a complete virus.